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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
PARKIN, J	
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DATE MAILED: 03/09/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/244,195	Kitto, G. And M. Burnett
Examiner	**Group Art Unit**
Jeffrey S. Parkin, Ph.D.	1648

X Responsive to communication(s) filed on *1 Dec 2000*

X This action is **FINAL.**

Since this application is in condition for allowance except for formal matters, **prosecution as to the merits** is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

X Claim(s) *1-3 and 5-11* is/are pending in the application

Of the above, claim(s) _____ is/are withdrawn from consideration.

Claim(s) _____ is/are allowed.

X Claim(s) *1-3 and 5-11* is/are rejected.

Claim(s) _____ is/are objected to.

Claims _____ are subject to restriction or election requirement.

Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The drawing(s) filed on _____ is/are objected to by the Examiner.

The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All ☐Some* ☐None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

X Notice of References Cited, PTO-892

Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

Interview Summary, PTO-413

Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Response to Amendment

Status of the Claims

1. Acknowledgement is hereby made or receipt and entry of the submission filed 01 December, 2000, wherein claims 1-3, 5-7, 9, and 10 were amended, claim 4 canceled without prejudice or disclaimer, and new claim 11 submitted. Accordingly, claims 1-3 and 5-11 are currently under examination.

35 U.S.C. § 112, First Paragraph

2. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 6-10 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants have amended the claims to specify that an attenuated bacterial host encoding an HIV-1 antigen is now being administered to an individual in need of such treatment. Applicants argue that the claimed methodology is fully enabled by the specification as illustrated by Examples 7-9. Applicants further argue that the Examiner has not provided any scientific evidence that the attenuated bacterial host would not be capable of initiating an HIV-1 specific immune response. These arguments are not deemed to be persuasive for the reasons of record previously set forth and as further elaborated below.

Applicants are reminded that the specification clearly states (pp. 1-2, bridging paragraph) that "The present invention relates to development of a **live vaccine for human immunodeficiency virus (HIV)**." The specification further states (p. 7, second paragraph) that "The present invention discloses development of a model **live vaccine for HIV**, using an attenuated strain of Salmonella engineered to surface express specific HIV proteins. In one embodiment, there is provided a **live vaccine for human immunodeficiency virus** comprising a recombinant plasmid containing genes required for surface exposure and a gene encoding a human immunodeficiency virus protein." Thus, the focus of the invention as set forth in the specification, is to provide vaccines for the treatment or prevention of HIV infection. Accordingly, the Examiner is assuming that the purpose of the immune response is to generate a protective or therapeutic response in the "individual in need of such treatment". Presumably, this is a human being who is infected with HIV-1 or an individual who is in a high-risk group and would need a vaccine to prevent infection. Accordingly, the disclosure would need to provide suitable support for this embodiment. However, as previously set forth, the disclosure is not enabling for a protective or therapeutic immune response in patients.

Contrary to applicants' assertions, sufficient evidence was provided by the Office demonstrating that HIV-1 vaccines are not functional (Haynes, 1993; Graham and Wright, 1995; Haynes, 1996; Lee, 1997). Applicants are directed toward the fifth point of the last Office action wherein it was clearly stated that the prior art is unpredictable and teaches that HIV vaccine attempts have been unsuccessful to date due to a number of caveats including the following: **1) A lack of understanding of the correlates of protective immunity. 2) A lack of understanding of those molecular**

determinants or antigens governing such responses. 3) The ability of HIV to spread via cell-cell mechanisms. 4) The ability of HIV to reside in immuno-privileged sites such as the CNS. 5) The quasispecies nature of HIV results in immune escape. 6) Inadequate animal models exist for HIV. All of these elements have contributed to vaccine failure. As Lee (1997) reflects on the status of phase I and II clinical vaccine trials he concludes (left col., p. 608) that "It is generally recognized that candidate HIV vaccines that have been tested in clinical trials do not elicit long-lasting antibodies or CTL responses." Thus, the prior art clearly teaches that the development of HIV vaccines has been unsuccessful to date.

Applicants' suggestion that Examples 7-9 provide sufficient support for the claimed invention is not tenable in view of the prior art discussed *supra* and the other arguments previously raised. The examples referred to involve the administration of an attenuated *Salmonella typhimurium* (designated SL3261) containing either an HIV-1 Tat or RT expression vector to mice. While robust immune responses were obtained following the administration of the attenuated S. *typhimurium* strain, the murine system is not considered an art-recognized model for HIV vaccine development and is not predictive of clinical efficacy. Thus, the results obtained in this study, while promising, cannot be directly extrapolated to the human arena. This is due to a number of obvious genotypic/phenotypic differences between the murine host and humans.

Moreover, applicants' response failed to provide any declaratory or scientific evidence addressing many of the caveats previously raised. For instance, the disclosure fails to provide adequate guidance pertaining to the nature and specificity of those immune responses (i.e., humoral or cell-mediated) that are capable of

preventing or inhibiting HIV viral replication. The disclosure fails to provide adequate guidance pertaining to the molecular determinants modulating protective or therapeutic immune responses to HIV. The disclosure also fails to provide any guidance pertaining to the quasispecies nature of HIV-1 and -2. Finally, the disclosure fails to provide any working embodiments demonstrating that a subject has been successfully protected from viral infection or that any given embodiment of the clinical sequelae associated with HIV infection has been ameliorated. Accordingly, when all the aforementioned factors are considered *in toto*, it would clearly require undue experimentation from the skilled artisan to practice the claimed invention. Therefore, the rejection of the claims is maintained. Applicants may obviate the rejection by directing the claims (as appropriately supported by the specification) towards methods of inducing antibodies in a murine host by administering the attenuated bacterial strain of interest.

35 U.S.C. § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1, 2, and 11 are rejected under 35 U.S.C. § 102(b) as being anticipated by Hone *et al.* (1996). This teaching provides attenuated *Salmonella typhimurium* vaccine vectors containing expression vectors encoding *Escherichia coli* OmpA::HIV-1 gp120 fusion proteins. These Salmonella strains induced both mucosal and

systemic HIV-1 gp120-specific immune responses.

35 U.S.C. § 103(a)

6. The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103(a).

8. Claim 5 is rejected under 35 U.S.C. § 102(b) as anticipated by Hone *et al.* (1996) or, in the alternative, under 35 U.S.C. § 103 as

obvious over Hone *et al.* (1996). The teachings of Hone and colleagues were discussed *supra*. This publication describes the use of an S. *typhimurium* strain carrying a mutation in the *aro* locus. This attenuated bacterial strain appears to be the same strain described by Fouts *et al.* (1995, Construction and immunogenicity of *Salmonella typhimurium* vaccine vectors that express HIV-1 gp120, Vaccine, 13(17):1697-705) which was designated strain SL3261. Since the Patent Office does not have the facilities for examining and comparing applicants' claimed S. *typhimurium* strain SL3261 with the S. *typhimurium* strain employed by Hone *et al.* (1996), the burden is upon applicants to demonstrate the unobvious genotypic/phenotypic differences between the two strains. *In re Best*, 562 F.2d 1252, 195 U.S.P.Q. 430 (C.C.P.A. 1977). *Ex parte Gray*, 10 U.S.P.Q.2d 1922 (Bd. Pat. Appl. Int. 1989).

9. Claim 3 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Hone *et al.* (1996) in view of Goff and Tanese (1993) or Thimmig and McHenry (1993). Hone and colleagues (1996) do not describe attenuated S. *typhimurium* strains expressing the HIV-1 RT. However, both Goff and Tanese (1993) and Thimmig and McHenry (1993) describe the preparation of *Escherichia coli* expression vectors encoding the HIV-1 RT. However, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute the gp120 described by Hone *et al.* (1996) with the RT provided by Goff and Tanese (1993) or Thimmig and McHenry (1993). One of ordinary skill in the art would be motivated to express the HIV-1 RT in the S. *typhimurium* expression system described by Hone *et al.* (1996) since this provides a safe, inexpensive, and efficient means for the delivery of HIV antigens to the appropriate host. Such a system

would provide one of ordinary skill in the art with an efficient means for generating HIV-1-specific immunological reagents (i.e., antibodies, CTLs, etc.).

10. Claims 1-3, 5, and 11 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Brey *et al.* (1992) in view of Zenno and Inouye (1994) and Goff and Tanese (1993) or Thimmig and McHenry (1993). Brey *et al.* (1992) describe the preparation of S. *typhimurium* expression systems (including those derived from strain SL3261) that are useful for the expression of malarial antigens. This teaching does not disclose the utilization of an OmpA signal sequence or the expression of the HIV-1 RT. Zenno and Inouye (1994) teach that the inclusion of the E. *coli ompA* signal sequence in expression cassettes facilitates the production of large quantities of secretory proteins. As stated *supra*, Goff and Tanese (1993) and Thimmig and McHenry (1993) describe the preparation of *Escherichia coli* expression vectors encoding the HIV-1 RT. Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to express the HIV-1 RT provided by Goff and Tanese (1993) and Thimmig and McHenry (1993) in the S. *typhimurium* expression system described by Brey *et al.* (1992), since Brey and colleagues teach that this system is useful for generating strong immune responses against the antigen of interest. It would have also been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to prepare a fusion protein comprising OmpA and the RT since Zenno and Inouye (1994) teach that the inclusion of OmpA sequence facilitates the production of large quantities of secreted forms of the protein of interest. One of ordinary skill in the art would have been motivated to incorporate such a sequence into an OmpA/RT fusion protein since the RT is not normally

secreted. The inclusion of a signal sequence would reasonably be expected to increase the secreted quantities of the RT thereby simplifying purification or increasing the immunogenicity of the protein.

Finality of Office Action

11. Applicant's amendment necessitated any and all new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL.** See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a). **A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.**

Correspondence

12. Correspondence related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Official communications should be directed toward one of the following Group 1600 fax numbers: (703) 308-4242 or (703) 305-3014. Informal communications may be submitted directly to the Examiner through the following fax number: (703) 308-4426. Applicants are encouraged to notify the Examiner prior to the submission of such documents to facilitate their expeditious processing and entry.

13. Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (703) 308-

2227. The examiner can normally be reached Monday through Thursday from 8:30 AM to 6:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisors, James Housel or Laurie Scheiner, can be reached at (703) 308-4027 or (703) 308-1122, respectively. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

Respectfully,

Jeffrey S. Parkin, Ph.D.
Patent Examiner
Art Unit 1648

09 February, 2001

LAURIE SCHEINER
PRIMARY EXAMINER

NOTES

- Serious vaccine enablement issues are present. Amendment of the claim language will not produce an allowance due to the large amount of art available on salmonella as a vaccine delivery vehicle.

- "The present invention relates to development of a live vaccine for human immunodeficiency virus (HIV)." (pp. ½, bridging para.)

- "The present invention discloses development of a model live vaccine for HIV, using an attenuated strain of Salmonella engineered to surface express specific HIV proteins. In one embodiment, there is provided a live vaccine for human immunodeficiency virus comprising a recombinant plasmid containing genes required for surface exposure and a gene encoding a human immunodeficiency virus protein." (p. 7, second para.)

- "In one embodiment of the present invention, there are provided recombinant plasmids, containing the Lpp-OmpA genes required for surface exposure, followed by the genes for the HIV-1 proteins, Reverse Transcriptase, or Transactivating protein (Tat). In a preferred embodiment, the plasmids are electroporated into an attenuated strain of Salmonella, SL3261." (p. 7, third para.)

DATA

- Used attenuated Salmonella SL3261; fusion protein comprising E. coli lipoprotein signal sequence (lpp) (aa 1-9) linked to the E. coli outer membrane protein ompA (aa 46-159)

- Made lpp-ompA-Tat (HIV-1) and lpp-ompA-RT (HIV-1)??? fusions

- Electroporate said constructs into Salmonella SL3261

- Immunized Balb/C mice with attenuated Salmonella

- IgA response observed in mice; splenocyte proliferative responses to immunizing Ag also observed;

ART

- The prior art appears strong since the construct and antigen of interest were all well-known in the PA.